REMARKS

Reconsideration and withdrawal of the rejections set forth in the Office Action dated October 18, 2004 are respectfully requested.

I. Amendments

Claim 1 is amended to recite that L is a phospholipids that has a head group attached to the dithiobenzyl moiety. Basis is found on page 9, line 34 to page 10, line 2 (describing a phospholipid having a head group); on page 10, lines 27-29 (describing that L is suitable for incorporation into a liposome lipid bilayer, intending that the hydrophobic tail portion be available for insertion into a lipid bilayer); and in Fig. 9A, (where attachment of a distearoyl lipid at its head group to the DTB moiety is shown).

II. Rejection Under 35 U.S.C. §103

Claims 1-2, 7-12, and 15 were rejected under 35 U.S.C. §103 as being obvious over EP 317 956 in view of Waalkes *et al.* (*Selective Cancer Therapeutics*, 6(1):15 (1990)), [sic] Diaz *et al* (*Bioconjugate Chem.*, 9:250 (1998)). This rejection is respectfully traversed for the following reasons.

A. The Present Invention

The present invention relates to a conjugate, and to compositions containing the conjugate, comprised of a phospholipid joined to a therapeutic drug by a dithiobenzyl (DTB) moiety, where the phospholipid is attached to the DTB moiety at its head group.

B. The Cited Art

EP 317 956 describes a prodrug of the form R^3-DTB-drug, where R^3 is an organic functional group selected from, for example, alkyl, phenyl, heteroaryl, (page 3, lines 29-41).

Waalkes *et al.* describe a di-acylated prodrug for enhanced retention of the drug near target cells. The prodrug consists of dipalmitoyl attached to the drug fluoro-deoxyuridine (FUdR) by an ester bond, which has a relatively slow cleavage for generation of the drug in active form.

Diaz *et al.* describe a protein-phospholipid conjugate, where the protein is coupled to the fatty acyl chain of the lipid in order to preserve the integrity of the lipid head group.

C1. Analysis: Combination of EP with Waalkes *et al*: Obviousness Requires a Motivation to Combine

According to the MPEP § 2143, "to establish a prima facie case of obviousness, ... there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. "

As noted above, the present claims relate to a phospholipid-DTB-drug conjugate, where the head group of the phospholipid is attached to the DTB moiety.

The Examiner asserts it would be obvious to modify EP 317 956 to use a phospholipid as the organic functional group (R^3 in the EP 317 956 structure) in view of the teaching in Waalkes *et al.* that phospholipids form liposomes, which are drug carriers offering enhanced drug retention. In fact, as noted by Waalkes *et* al. the drug with which Waalkes *et al.* are concerned, fluoro deoxyuridine (FUdR), is not well retained in liposomes (page 16, first full paragraph). To solve this problem, Waalkes *et al.* modify the drug to include an diacyl tail, such as di-palmitic acid. The diacylated FUdR is then incorporated into liposomes, to provide retention of the FUdR in liposomes.

The drug-lipid conjugate of Wallkes *et al.* is not a drug-phospholipid conjugate, but a drug-fatty acid conjugate. While Waalkes *et al.* disclose phospholipids for forming liposomes, as do any number of other references in the prior art, there is no

suggestion in Waalkes *et al.* to use a phospholipid in place of the fatty acid in the drug-fatty acid conjugate.

Nor do Waalkes *et al.* provide a source of motivation to modify EP 317 956. EP 317 956 is not concerned with liposomes or with phospholipids, but with a prodrug that is less cytotoxic to tumor cells compared to the parent drug and that can be enzymatically converted into the more active parent drug. Absent Applicants' own teaching of a phospholipid-drug conjugate, there is nothing in the EP 317 956 and Waalkes *et al.* references that would stimulate one to take the phospholipid from the liposomes in Waalkes *et al.* and place in the prodrug of EP 317 956. Accordingly, withdrawal of the rejection is respectfully requested.

C2. Analysis: Combination of EP with Diaz *et al*: Obviousness Requires a Showing of All Claim Elements

According to the MPEP § 2143, "to establish a prima facie case of obviousness, ... the prior art references (or references when combined) must teach or suggest all the claim limitations."

As noted above, the present claims relate to a phospholipid-DTB-drug conjugate, where the head group of the phospholipid is attached to the DTB moiety.

EP 317 956 fails to show or suggest a phospholipid joined to a DTB-drug moiety. Diaz *et al.* show a protein-phospholipid conjugate, where the protein is attached to the fatty acyl tail of the phospholipid (see Fig. 1) in order to preserve the head group for development of antibodies against the phospholipid (page 250).

Thus, the combination of teachings fails to show or suggest all the claim elements, namely a phospholipid attached at its head group to a DTB moiety. Withdrawal of the rejection is respectfully requested.

III. Conclusion

In view of the foregoing, the claims pending in the application comply with the requirements of 35 U.S.C. § 112 and patentably define over the applied art. A Notice of Allowance is, therefore, respectfully requested. If the Examiner has any questions or

believes a telephone conference would expedite prosecution of this application, the Examiner is encouraged to call the undersigned at (650) 838-4402.

Respectfully submitted,

Date: January 12, 2005

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